Influence of Calculation Level and Effect of Methylation on Axial/Equatorial Equilibria in Piperidines

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ABSTRACT: A detailed conformational analysis was performed on the chair forms of piperidine, *N*-methylpiperidine, and some methylated derivatives using Hartree–Fock (HF) and MP2 *ab initio* methods with several basis sets (from 3–21G to 6–311 + + G**), and the most widely used semiempirical approaches (MNDO, AM1, and PM3). It was found that the use of polarized basis sets at the HF level is adequate enough for the prediction of conformational preferences in the axial/equatorial equilibrium of the N-R group in piperidines. On the other hand, the inclusion of electron correlation becomes necessary for predicting the axial/equatorial energy differences of the equilibria of the methyl group. Semiempirical methods are not recommended, because AM1 and PM3 predict opposite stabilities to those obtained experimentally and MNDO ring geometries are systematically too flat. The origin of the conformational stabilities was interpreted in terms of the natural bond orbital analysis of the HF/6–31G** wave functions. The equatorial preferences in the N-H equilibria is mainly due to lower Lewis energies, although delocalization of the nitrogen lone pair is favored in N-H axial forms. *N*-Methylation increases the equatorial M-Me preferences, because the Lewis energy of axial N-Me forms increases due to larger 1,3-diaxial interactions. Geometrical trends associated with the delocalization of the nitrogen lone pair and with interactions between the introduced N-R and C-Me groups were discussed and related to the degree of planarity of the six-membered ring by means of the puckering coordinates defined by Pople and Cremer. J Comput Chem 19: 961–976, 1998

Keywords: piperidine; *ab initio* methods; natural bond orbital analysis; hyperconjugation; puckering coordinates

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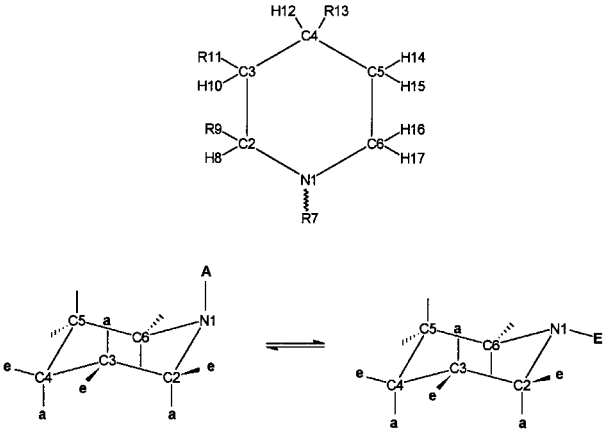
Introduction

Piperidine rings and their derivatives form part of numerous organic compounds of biological interest, such as alkaloids and opiates, and thus their conformational axial/equatorial equilibrium has long been studied.[1-12] Experimentally, piperidine has been studied mainly by means of indirect techniques, such as δ_{ae} measurements in ^{1}H NMR,[1] dipole moment determinations,[2] analysis of Bohlman bands in the IR spectrum,[3] dynamic ^{13}C NMR spectra,[4] or calorimetric measurements.[5] After a long controversy,[9,10] the equatorial preference of the N-H group was definitively established, taking $\Delta G^\circ = 0.4 \pm 0.2$ kcal/mol as an average value.[10] More recently, by means of microwave spectroscopy, this value was increased to 0.74 ± 0.07 kcal/mol.[12] The mono- and polymethyl derivatives of piperidine have also been the subject of study.[13-24] Among them, *N*-methylpiperidine has been the most widely analyzed; the equatorial preference of the N-Me group has never been questioned, although the published experimental data vary from 0.4 to 3.2 kcal/mol,[13-19] and values near the larger number are the most likely. The experimental data available for the piperidine rings have been used for the parametrization of the amines in the molecular mechanics programs MM2[25] and MM3.[26]

During the last years some theoretical research has been carried out on piperidine and *N*-methylpiperidine to complement studies on other series of molecules.[27-31] This research reproduces the experimental preferences of the equatorial conformers, apart from revealing geometrical variations in the C—H and C—C bonds as a consequence of the delocalization of the nitrogen lone pair.[27,32] However, to our knowledge, no theoretical study has been devoted to the influence of substitution in the piperidine ring. Therefore, we performed a complete *ab initio* conformational analysis of all the methylated derivatives of piperidine and *N*-methylpiperidine, establishing the influence of substitution on the different positions of the ring. The influence of the quality of the basis set is discussed, as well as the importance of considering electron correlation for a proper description of these systems. The most widely used semiempirical methods were also employed to determine their reliability in the study of these compounds, mainly due to the fact that their use is essential for the study of larger biological molecules, which are impossible to handle by means of *ab initio* methods because of computational limitations.[31] On the other hand, as the nitrogen lone pair delocalizes on the bonds in the trans orientation, the natural bond orbital (NBO) analysis [33-37] of the obtained wave functions was performed, because this method has recently been successfully used in the interpretation of the anomeric effect in which electron delocalization also plays an important role.[38-41]

Computational Details

Figure 1 shows all the compounds included in this study. Piperidine (**1**) and *N*-methylpiperidine (**1m**) have two possible chair conformations, which differ in the axial (A) or equatorial (E) position of



N1 = C1 R7, R9, R11, R13 = H	Methylcyclohexane	**0me**	**0ma**		
R7 = H R9, R11, R13 = H	Piperidine	**1E**	**1A**		
R7 = Me R9, R11, R13 = H	N-methylpiperidine	**1mE**	**1mA**		
R7 = H, R9 = Me R11, R13 = H	2-methylpiperidine	**2Ee**	**2Ea**	**2Ae**	**2Aa**
R7 = H, R11 = Me R9, R13 = H	3-methylpiperidine	**3Ee**	**3Ea**	**3Ae**	**3Aa**
R7 = H, R13 = Me R9, R11 = H	4-methylpiperidine	**4Ee**	**4Ea**	**4Ae**	**4Aa**
R7 = Me, R9 = Me R11, R13 = H	N,2-dimethylpiperidine	**2mEe**	**2mEa**	**2mAe**	**2mAa**
R7 = Me, R11 = Me R9, R13 = H	N,3-dimethylpiperidine	**3mEe**	**3mEa**	**3mAe**	**3mAa**
R7 = Me, R13 = Me R9, R11 = H	N,4-dimethylpiperidine	**4mEe**	**4mEa**	**4mAe**	**4mAa**

FIGURE 1. Atom numbering and notation employed for the compounds studied in the present work.

the N-R group. Other conformations that differ from the chair (boat, envelope, or twist boat) were not considered because of their high energy. The methyl derivatives in positions C2, C3, and C4 of the ring can have four chair conformations characterized by the relative orientations of the N-R group (A or E) and of the C-Me group (a or e). Calculations performed for cyclohexane (**0**) and methylcyclohexane (**0m**) were also included to analyze the differences between the ring with only carbon atoms and those including the heteroatom.

All the compounds were completely optimized at the Hartree–Fock (HF) level using the 3–21G and 6–31G** basis sets. Cyclohexane, methylcyclohexane, N-H compounds (**1**, **2**, **3**, and **4**), and *N*-methylpiperidine were also optimized at the MP2/6–31G** level. Single-point calculations were performed on the optimized geometries using the 6–311G**, 6–31+G**, 6–31++G**, and 6–311++G** basis sets, because the importance of diffuse functions in the basis set to correctly describe systems with lone electron pairs was suggested.[42,43] All the conformers were characterized as minima by means of the analysis of their vibration frequencies, and the HF/6–31G** zero point energy (ZPE) was calculated.

NBO analysis[33–37] was performed on the HF/6–31G** wave functions obtained for the geometries optimized with that specific basis. The NBO program transforms the HF molecular orbitals in a set of localized orbitals called NBOs, which form a hypothetical Lewis structure with strictly localized electron pairs. In the NBO basis, delocalization arises from interactions between occupied bond orbitals and antibond orbitals and are represented by off-diagonal terms in the Fock matrix. For the evaluation of these interactions, the NBO deletion procedure was used in which all off-diagonal terms in the Fock matrix are eliminated and only one self-consistent field (SCF) cycle is computed. The energy obtained is called Lewis energy (E_{Lew}) and corresponds to a hypothetical molecule with localized bonds. The difference between E_{Lew} and the SCF total energy (E_{rel}) corresponds with the energy contributions of all the interactions between orbitals, in other words, the delocalization energy of the molecule, E_{del}. The interactions $n_{\mathrm{N}}-\sigma^{*}_{\mathrm{C-H}}$ and $n_{\mathrm{N}}-\sigma^{*}_{\mathrm{C-C}}$ are dominant, but smaller interactions between adjacent bonds and antibonds must also be taken into account and can have different relative contributions to E_{del} for each conformer. For carrying out the *ab initio* calculations and the NBO analysis, the Gaussian 94 program was used.[44] All the conformers were also studied with the semiempirical methods AM1, PM3, and MNDO using Spartan 4.1.[45]

The puckering coordinates of Cremer and Pople[46] were calculated for the optimized geometries, because they are a useful tool for the description of rings using a reduced number of parameters and serve to illustrate the geometrical effects associated with substitution. Briefly, the Q coordinate represents the puckering amplitude and the values of θ and ϕ_2 indicate the deformation of the chair conformation of the ring. Thus, for a perfect chair, coordinates $\theta = 0°$ and $\phi_2 = 0°$ are expected. Different values of θ and ϕ_2 indicate the mixing of the chair with the different boat ($\theta = 90°$; $\phi_2 = 0$, 60, 120, 180, 240, or 300°) or twist-boat ($\theta = 90°$; $\phi_2 = 30$, 90, 150, 210, 270, or 330°) forms that are possible for the piperidine ring.

Results and Discussion

INFLUENCE OF CALCULATION LEVEL ON ENERGY DIFFERENCES AND GEOMETRIES

Table I shows the *ab initio* relative energies obtained at various computational levels for all the compounds studied. In agreement with the experimental data, the equatorial form of piperidine (**1**E) was always found to be the most stable. At the HF level, the N-H axial/equatorial energy difference, $\Delta E_{\mathrm{A/E}}$, shows noticeable discrepancies between the 3–21G (0.32 kcal/mol) or 4–21G (0.1 kcal/mol)[27] values and those obtained with larger basis sets. However, the HF relative energies obtained with 6–31G** to 6–311++G** are almost independent of the basis set employed.[47] According to this, in order to calculate $\Delta E_{\mathrm{A/E}}$ it seems necessary to include polarization in the basis set, but not so much to increase its size or to add diffuse functions. At the MP2 level $\Delta E_{\mathrm{A/E}}$ oscillates, which suggests that this method is more dependent on the basis set than HF. Nevertheless, HF and MP2 energy differences converge with the largest basis used, 6–311++G** (0.85 kcal/mol). The inclusion of ZPE increases the axial preference by 0.1 kcal/mol, so the best theoretical value (MP2/6–311++G**//MP2/6–31G**+ZPE) for $\Delta E_{\mathbf{1A/1E}}$ is 0.76 kcal/mol, which is in excellent agreement with the experimental value of 0.74 ± 0.07 obtained by microwave spectroscopy.[12] Also in agreement with the experiment, the N-Me group in *N*-methylpiperidine notably increases the preference for the equatorial form (**1m**E) (Table I). As in **1**, HF results depend very slightly on the basis

TABLE I.
Relative Energies[47] at Various Computational Levels for Conformers of Methylcyclohexane (0m), N-H Compounds (1–4), and N-Me Compounds (1m–4m).

	HFB0	HFB1	HFB2	MP2B1		MP2B2	Th	Exptl
0me	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0
0ma	1.92	2.31	2.32	1.78	1.86	1.61	1.82	1.75 (ref. 48), 1.9–2.0 (ref. 49)
1E	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0
1A	0.32	0.76	0.86	0.54	0.50	0.85	0.76	0.74 ± 0.07 (ref. 12)
2Ee	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0
2Ae	0.44	0.88	0.95	0.78	0.74	1.05	0.97	
2Ea	2.17	3.07	3.13	2.74	2.81	2.85	2.99	2.5 (ref. 24)
2Aa	2.55	3.53	3.62	3.00	3.05	3.17	3.30	
3Ee	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0
3Ae	0.25	0.67	0.74	0.42	0.39	0.70	0.63	
3Ea	0.66	1.57	1.78	0.93	1.01	1.10	1.27	1.6 (ref. 24)
3Aa	1.58	2.62	2.78	1.85	1.87	2.10	2.21	
4Ee	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0
4Ae	0.25	0.72	0.79	0.46	0.42	0.71	0.62	
4Ea	1.96	2.46	2.51	2.03	2.10	1.93	2.13	1.9 (ref. 24), 1.93 (ref. 23)
4Aa	2.26	3.17	3.30	2.46	2.50	2.66	2.78	
1mE	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1mA	2.01	3.59	3.91	3.18	3.23	3.67	3.70	3.16 ± 0.10 (ref. 19)
2mEe	0.00	0.00	0.00		0.00	0.00	0.00	0.0
2mEa	0.48	1.47	1.66		1.80	2.17	2.15	1.7 (ref. 24)
2mAe	1.48	2.83	3.14		2.70	3.21	3.25	
2mAa	1.80	3.54	3.88		3.59	4.11	4.13	
3mEe	0.00	0.00	0.00		0.00	0.00	0.00	0.0
3mEa	0.69	1.56	1.79		0.93	1.08	1.26	1.51 (ref. 21), 1.6 (ref. 24)
3mAe	1.91	3.51	3.82		3.10	3.51	3.55	
3mAa	5.18	7.16	7.52		6.42	6.77	6.92	
4mEe	0.00	0.00	0.00		0.00	0.00	0.00	0.0
4mEa	1.88	2.39	2.45		1.96	1.91	2.11	1.8 (ref. 24), 1.99 (ref. 21)
4mAe	1.93	3.54	3.85		3.06	3.51	3.56	
4mAa	3.99	6.09	6.46		5.23	3.65	3.90	

See notation of conformers in Figure 1.
Computational levels employed in this work are: HFB0, HF/3–21G//HF/3–21G; HFB1, HF/6–31G**//HF/6–31G**; HFB2, HF/6–311++G**//HF/6–31G**; MP2B1, MP2/6–31G**//MP2/6–31G** (first column); MP2/6–31G**//HF/6–31G** (second column); MP2B2, MP2/6–311++G**//MP2/6–31G** for **0m**, **1**–**4**, and **1m**; MP2/6–311++G**//HF/6–31G** for **2m**–**4m**; Th, MP2B2 + ZPE HF/6–31G**; Exptl, experimental data.

set (except 3–21G) and are quite similar to the MP2 values. ZPE hardly influences the axial/equatorial energy difference, so the best theoretical prediction for $\Delta E_{\mathbf{1m}\mathrm{A}/\mathbf{1m}\mathrm{E}}$ would be 3.70 kcal/mol, which is slightly larger than the highest experimental estimation of 3.15 kcal/mol obtained by ^{13}C NMR in the gas phase.[19]

In the methylated derivatives of piperidine, 2-methyl- (**2**), 3-methyl- (**3**), and 4-methylpiperidine (**4**) one can consider both the axial/equatorial equilibrium of the N-H group (pairs of conformers Ae/Ee and Aa/Ea) and the axial/equatorial equilibrium of the C-Me group in the methylation position (pairs Ea/Ee and Aa/Ae). The results obtained for methylcyclohexane would be the reference for the C-Me equilibrium. The HF axial/equatorial energy differences for **0m**, $\Delta E_{a/e}$, are almost independent of the basis (except 3–21G), and the MP2 values are always below the HF ones (Table I). According to this, the preference for the C-Me equatorial forms is overestimated by approximately 0.5 kcal/mol at the HF level. ZPE acts in the opposite direction and stabilizes the equatorial form by 0.2 kcal/mol, so that the highest theoretical value obtained of $\Delta E_{\mathbf{0m}\mathrm{A}/\mathbf{0m}\mathrm{E}}$(MP2/6–311G ++G**//MP2/6–31G** + ZPE) = 1.82 kcal/mol agrees remarkably well with the experimental value of 1.75 kcal/mol obtained by NMR spectroscopy in solution[48] and with the gas phase value of[49] 1.9–2.0 kcal/mol.

As in **1**, the N-H equatorial form is the most stable in compounds **2**, **3**, and **4**. The energy differences for the N-H equilibria (pairs Ae/Ee) and for the C-Me equilibria (pairs Ea/Ee) show variations with the calculation level similar to those of **1** and **0m**, respectively. According to this, we can conclude that the HF axial/equatorial energy difference of the N-H equilibria is quite reliable even with a middle size basis set as 6−31G** while the MP2 corrections are very sensitive to the basis set and can be considered as artifacts. The same tendency was observed for other heterocyclic systems.[38] MP2 calculations, however, are necessary to correctly describe the equilibrium of the C-Me group and correct the overestimation of the Me-equatorial form at the HF level.

Because of computational limitations and the increase in size, *N*,2-dimethyl- (**2m**), *N*,3-dimethyl- (**3m**), and *N*,4-dimethylpiperidine (**4m**) were optimized at the HF/3−21G and HF/6−31G** levels only. In spite of this, it should be noted that the MP2/6−31G**//HF/6−31G** and MP2/6−31G**//MP2/6−31G** results for **0m**, compounds **1**−**4**, and **1m** are almost identical (column MP2B1 of Table I), so MP2 single point energies seem to be sufficiently reliable and insensitive to geometry optimization. The N-Me compounds also show the double equatorial form as the most stable; in contrast to what happened for **2**, **3**, and **4**, *N*-methylation determines the energy ordering Ee < Ea < Ae < Aa, because the conformers with N-Me in the equatorial position are more stable. The influence of the calculation level on the description of the N-Me and C-Me equilibria is similar to that indicated for **1m** and **0m**, except for **2m** for which the MP2 relative energies for **2m**Ea and **2m**Aa are approximately 0.5 kcal/mol higher than the HF ones. The only experimental data available for **2**−**4** and its *N*-methyl derivatives **2m**−**4m** correspond with the energy differences of the C-Me group equilibria (pairs Ea/Ee).[20−24] In any case, the agreement between experimental and theoretical results is quite good, and average differences were of the order of ± 0.5 kcal/mol.

In Table II some selected parameters for the HF/3−21G, HF/6−31G**, and MP2/6−31G** optimized geometries of cyclohexane, piperidine, and *N*-methylpiperidine are shown. At the HF level, the increase of the size of the basis set and, in particular, the introduction of polarization makes the electron density increase in the bond region.[50,51] As a consequence of this, when going from HF/3−21G to HF/6−31G** geometries, the C—C and C—N bonds shorten and the adjacent bonds repel each other more strongly, so that the bond angles open and the endocyclic torsions decrease (see C−C−C and C−C−N angles and C−C−C−C, C−N−C−C, and C−C−C−N torsional angles in Table II). These geometrical variations produce the flattening of the ring and the puckering amplitude Q is reduced. When electron correlation is considered at the MP2 level, the electron density is redistributed, increasing around the nuclei and diffuse regions of the molecule, while the density decreases in the bond region so that steric repulsions decrease.[50,52] According to this, the MP2/6−31G** geometries show shorter C—C bonds than the HF/6−31G** ones, but delocalization of bonding electrons lengthens the C−N bonds. Bond angles tend to close and torsional angles open (see Table II), which leads to an MP2-optimized ring that is slightly puckered in comparison with the HF one and Q increases. Furthermore, the puckering amplitude Q varies as $Q(6-31G^{**}) < Q(MP2) < Q(3-21G)$ for all the compounds studied (see Table III) (i.e., for rings of carbon atoms and containing nitrogen, in contrast to what happened to the energy variations where the inclusion of electron correlation yielded different results). Therefore, the behavior of Q is related to the calculation level and not to the system under study.

The differences between some geometrical parameters of the axial and equatorial forms of piperidine could be related to the delocalization of the nitrogen lone pair.[32] It has been established that the bonds in trans orientation to the lone pair are lengthened, and the angles that these bonds form are opened. Thus, in the equatorial N-R conformers of **1** and **1m**, the H9—C2 bonds are lengthened and the angles H9−C2−N1 are opened in comparison with their values in the axial forms (Table II). On the other hand, the axial N-R conformers show larger C2—C3 bonds and N1−C2−C3 angles, because they are trans disposed to the nitrogen lone pair. Although the HF and MP2 absolute values of the geometrical parameters are different, the axial/equatorial differences are similar and the geometrical tendencies associated with the delocalization of the lone pair are suitably described using any computational level. Therefore, even though MP2 optimizations are intrinsically more correct, even the HF/3−21G method provides a proper description of the geometrical trends in the cyclic systems studied in this work. Due to this, from now on the discussion will be based on HF/6−31G** geometries, the highest theoretical level used for geometry optimization in all the compounds.[53]

TABLE II.

Optimized Geometries and Pople and Cremer's Puckering Coordinates for Cyclohexane (0), Methylcyclohexane (0m), Piperidine (1) and *N*-methylpiperidine (1m).

	HF/3-21G		HF/6-31G**		MP2/6-31G**	
Cyclohexane	**0**		**0**		**0**	
C1-C2	1.5411		1.5318		1.5283	
C1-C2-C3	110.73		111.46		111.17	
H9-C2-C1	109.19		109.19		109.05	
C1-C2-C3-C4	56.79		54.75		55.57	
H9-C2-C1-C6	63.46		65.97		64.70	
Q (Å)	0.589		0.561		0.569	
ϕ_2 (°)	0.00		0.00		0.00	
θ (°)	0.00		0.00		0.00	
Methylcyclohexane	**0me**	**0ma**	**0me**	**0ma**	**0me**	**0ma**
C1-C2	1.5410	1.5450	1.5347	1.5391	1.5298	1.5345
C2-C3	1.5410	1.5416	1.5312	1.5328	1.5280	1.5295
C3-C4	1.5404	1.5402	1.5307	1.5312	1.5275	1.5281
C7-C1	1.5386	1.5413	1.5287	1.5336	1.5243	1.5286
C1-C2-C3	111.51	112.52	112.20	113.16	112.01	112.60
C6-C1-C2	109.76	110.01	110.33	110.00	110.11	109.87
C7-C1-C2	110.88	111.91	111.60	112.51	111.51	112.11
H9-C2-C1	108.68	108.75	108.54	108.96	108.68	108.55
C1-C2-C3-C4	56.97	56.06	55.05	54.52	55.81	55.47
C2-C3-C4-C5	−56.44	−56.99	−54.51	−54.68	55.42	55.52
C6-C1-C2-C3	−56.39	−53.73	−54.42	−52.70	−55.05	−54.06
Q (Å)	0.587	0.575	0.560	0.552	0.568	0.564
ϕ_2 (°)	0.00	180.00	0.00	180.00	180.00	180.00
θ (°)	0.00	2.38	0.00	1.31	0.20	0.91
Piperidine	**1**E	**1**A	**1**E	**1**A	**1**E	**1**A
N1-C2	1.4703	1.4730	1.4525	1.4543	1.4628	1.4646
C2-C3	1.5354	1.5419	1.5264	1.5318	1.5236	1.5297
C3-C4	1.5411	1.5425	1.5311	1.5317	1.5280	1.5280
H7-N1	1.0042	1.0061	1.5311	1.5317	1.0152	1.0176
H9-C2	1.0927	1.0847	1.0964	1.0884	1.1032	1.0948
N1-C2-C3	108.70	112.59	109.69	113.69	109.09	114.03
C6-N1-C2	113.51	113.03	112.92	112.76	110.00	111.22
H7-N1-C2	112.89	112.06	110.37	109.74	109.16	108.30
H9-C2-N1	112.22	107.61	112.15	107.72	112.43	107.18
N1-C2-C3-C4	57.06	54.66	55.90	53.27	57.77	54.37
C2-C3-C4-C5	−55.55	−55.19	−52.57	−52.64	−53.37	−53.52
C6-N1-C2-C3	−61.70	−54.51	−61.45	−53.36	−63.79	−53.72
H9-C2-N1-C6	58.95	65.86	59.89	67.93	57.00	67.26
Q (Å)	0.594	0.558	0.572	0.533	0.594	0.542
ϕ_2 (°)	0.00	180.00	0.00	180.00	0.00	180.00
θ (°)	1.42	3.44	3.28	2.69	4.88	2.53

(Continued)

TABLE II.
(Continued)

	HF/3–21G		HF/6–31G**		MP2/6–31G**	
N-Methylpiperidine	**1m**E	**1m**A	**1m**E	**1m**A	**1m**E	**1m**A
N1–C2	1.4695	1.4691	1.4523	1.4542	1.4606	1.4638
C2–C3	1.5346	1.5435	1.5257	1.5338	1.5228	1.5317
C3–C4	1.5388	1.5426	1.5287	1.5320	1.5258	1.5287
C7–N1	1.4640	1.4643	1.4446	1.4470	1.4543	1.4560
H9–C2	1.0940	1.0856	1.0981	1.0887	1.1063	1.0952
N1–C2–C3	110.12	112.75	111.09	114.05	110.67	114.23
C6–N1–C2	112.62	112.05	112.05	111.51	110.37	110.33
C7–N1–C2	113.00	115.20	111.99	114.43	110.44	112.80
H9–C2–N1	111.24	107.88	111.18	107.68	111.08	107.27
N1–C2–C3–C4	57.01	55.45	55.84	54.06	57.53	55.08
C2–C2–C4–C5	−55.60	−54.97	−52.68	−52.41	−53.46	−53.50
C6–N1–C2–C3	−59.54	−55.75	−59.25	−54.40	−61.31	−54.72
H9–C2–N1–C6	62.01	64.45	62.92	66.39	60.50	65.85
Q (Å)	0.585	0.564	0.563	0.538	0.582	0.548
ϕ_2 (°)	0.00	180.00	0.00	180.00	0.00	180.00
θ (°)	0.00	2.46	1.80	1.70	3.16	1.79

Bond lengths are in angstroms; bond and torsional angles are in degrees.

The results obtained by using semiempirical methods are shown in Table IV. Relative energies show remarkable differences, depending on the semiempirical method employed, and are also different from the *ab initio* values. Surprisingly, AM1 and PM3 predict that the N-H and N-Me axial forms are more stable in contrast to the *ab initio* energy ordering. However, MNDO reproduces the *ab initio* stabilities (except **2m**), although both N-H and N-Me axial forms are overestimated (~ 0.3 and ~ 2.4 kcal/mol, respectively, compared to the Th values in Table II). On the other hand, the C-Me equatorial preference of **0m** is correctly reproduced by all the semiempirical methods, even though the energy differences also indicate an overestimation of the Me-axial forms by ~ 0.4 kcal/mol (AM1), ~ 0.7 kcal/mol (PM3), and ~ 0.8 kcal/mol (MNDO).

The semiempirical puckering coordinates also show differences between methods. For cyclohexane, AM1 and HF/6–31G** predict a similar chair ($Q = 0.560$ and 0.561 Å, respectively), while PM3 puckers it slightly (0.572 Å). The small MNDO value is surprising (0.465 Å), representing a chair that is approximately 15% flatter than the HF/6–31G** one. The tendencies are similar for **0m**. With respect to the piperidine rings, the AM1 structures are, on average, 5% flatter than the corresponding HF/6–31G** ones; this effect was more pronounced in the N-H and N-Me equatorial forms. PM3 geometries agree quite well with the *ab initio* ones and the differences between the values of Q are about $\pm 1\%$. Finally, although the MNDO energies reproduced the *ab initio* values acceptably, the Q amplitudes are again small and the MNDO piperidine chairs are approximately 15% flatter than HF/6–31G**. According to these results, the larger flattening of the MNDO rings considerably reduces the 1,3-diaxial repulsions and probably for this reason the energy ordering coincides with that obtained by *ab initio* methods, while AM1 and PM3 geometries are correct at the cost of increasing their energy.

INFLUENCE OF NITROGEN ATOM: COMPARISON BETWEEN CYCLOHEXANE AND PIPERIDINE RINGS

A comparison between the optimized geometries of cyclohexane and both chair forms of piperidine provides information about the effect of the heteroatom. The puckering amplitudes (Table II) indicate that the conformers of piperidine are placed ''at both sides'' of cyclohexane, (i.e., **1A** is flatter than cyclohexane, while **1E** is more puckered). However, the C2–C3–C4–C5 torsional angle is reduced in both forms with respect to the value in cyclohexane (Table II), which indicates that the C4 region of the piperidine ring is flattened. So, the N-H region determines the global puckering of

TABLE III.
Pople and Cremer's Puckering Coordinates for Conformers of Cyclohexane (0), Methylcyclohexane (0m), N-H Compounds (1–4), and *N*-Me Compounds (1m–4m) Obtained at Several *Ab Initio* Computational Levels.

	HF/3–21G			HF/6–31G**			MP2/6–31G**		
	Q (Å)	ϕ_2 (°)	θ (°)	Q (Å)	ϕ_2 (°)	θ (°)	Q (Å)	ϕ_2 (°)	θ (°)
0	0.589	0.00	0.00	0.561	0.00	0.00	0.569	0.00	0.00
0me	0.587	0.00	0.00	0.560	0.00	0.00	0.568	180.00	0.20
0ma	0.575	180.00	2.38	0.552	180.00	1.31	0.564	180.00	0.91
1E	0.594	0.00	1.42	0.572	0.00	3.28	0.594	0.00	4.88
1A	0.558	180.00	3.44	0.533	180.00	2.69	0.542	180.00	2.53
2Ee	0.591	347.46	1.08	0.570	356.57	2.98	0.592	355.33	4.66
2Ae	0.558	179.64	3.18	0.533	178.27	2.41	0.541	185.55	2.48
2Ea	0.575	245.42	2.78	0.557	299.75	1.95	0.580	331.17	2.91
2Aa	0.544	205.33	6.15	0.522	200.39	4.93	0.534	194.89	4.19
3Ee	0.592	0.25	1.67	0.571	1.79	3.39	0.592	357.55	5.18
3Ae	0.556	179.76	3.31	0.532	177.95	2.72	0.539	186.80	2.40
3Ea	0.591	1.13	3.71	0.571	6.83	4.73	0.596	7.16	6.04
3Aa	0.549	182.65	1.82	0.527	179.11	1.71	0.538	172.53	1.89
4Ee	0.592	0.00	1.47	0.571	0.00	3.18	0.592	0.00	5.12
4Ae	0.557	180.00	3.42	0.532	180.00	2.87	0.540	180.00	2.29
4Ea	0.580	0.00	3.93	0.563	0.00	4.95	0.588	0.00	6.47
4Aa	0.543	180.00	0.83	0.523	180.00	0.93	0.535	180.00	0.80
1mE	0.585	0.00	0.00	0.563	0.00	1.80	0.582	0.00	3.16
1mA	0.564	180.00	2.46	0.538	180.00	1.70	0.548	180.00	1.79
2mEe	0.585	270.39	0.72	0.563	336.29	1.77			
2mEa	0.572	206.29	1.70	0.553	41.45	0.54			
2mAe	0.570	85.66	0.33	0.546	22.90	1.10			
2mAa	0.551	212.63	4.64	0.529	208.93	3.56			
3mEe	0.583	359.89	0.19	0.562	2.903	1.92			
3mEa	0.582	19.73	2.60	0.562	11.76	3.44			
3mAe	0.562	180.21	2.43	0.538	180.24	1.78			
3mAa	0.547	239.06	4.98	0.524	237.09	4.77			
4mEe	0.583	0.00	0.00	0.563	0.00	0.00			
4mEa	0.572	0.00	2.51	0.554	0.00	3.51			
4mAe	0.562	180.00	2.53	0.538	180.00	1.86			
4mAa	0.548	0.00	0.25	0.528	0.00	0.26			

See notation for conformers in Figure 1.

the ring and $Q_{\mathbf{1A}}$ is smaller than $Q_{\text{cyclohexane}}$ because the region of the N-H group is also flattened, as suggested by $\phi_2 = 180$, which represents the mixing of the axial chair form with the inverted boat form.[46] **1E** is slightly puckered as result of the balance between the flattening in the C4 region and the puckering in the N-H region.

The behavior of the puckering coordinates is related to variations of different signs of some geometrical parameters when the N-H group is introduced in an axial or equatorial orientation in cyclohexane. Thus, the differences between the HF/6–31G** C1–C2–C3 angles of **0** and N1–C2–C3 of **1E** and **1A** are −1.77° and +2.23°, respectively. Furthermore, the H9–C2–N1 angle opens 3.03° in **1E** and closes −1.58° in **1A** when compared to the corresponding H9–C2–C1 angles of **0**. These geometrical variations were related above to the delocalization of the nitrogen lone pair. According to this, the degree of planarity of the conformers of piperidine is a consequence of delocalization, because the flattening of **1A** is due to the opening of the N1–C2–C3 angle, while in the equatorial form the nitrogen is slightly puckered because of the opening of the H9–C2–N1 angle.

Also related to the previous description, it is known that the experimental value of Q for cyclohexane (0.56 Å) is smaller than that expected for an ideal chair with standard C—C bonds, C–C–C tetrahedrical angles, and endocyclic dihedra of 60° (0.629 Å).[54] This reduction allows for the relief of

TABLE IV.
Relative Energies (E_{rel}) and Puckering Coordinates for Conformers of Cyclohexane (0), Methylcyclohexane (0m), N-H Compounds (1–4), and N-Me Compounds (1m–4m) Obtained by Using MNDO, AM1, and PM3 Semiempirical Methods.

	MNDO				AM1				PM3			
	E_{rel} (Kcal / mol)	Q (Å)	ϕ_2 (°)	θ (°)	E_{rel} (Kcal / mol)	Q (Å)	ϕ_2 (°)	θ (°)	E_{rel} (Kcal / mol)	Q (Å)	ϕ_2 (°)	θ (°)
0		0.465	0.00	0.00		0.560	0.00	0.00		0.572	0.00	0.00
0me	0.00	0.483	0.00	3.14	0.00	0.566	0.00	0.00	0.00	0.578	0.00	0.76
0ma	1.03	0.466	0.00	1.34	1.42	0.547	180.00	2.59	1.12	0.555	180.00	3.47
1E	0.00	0.477	0.00	5.38	2.73	0.526	180.00	4.51	2.24	0.565	180.00	0.84
1A	0.51	0.436	180.00	0.58	0.00	0.509	180.00	4.74	0.00	0.540	180.00	2.92
2Ee	0.00	0.490	19.71	5.69	3.06	0.540	143.18	2.41	2.35	0.575	64.58	1.09
2Ae	0.41	0.455	58.84	3.83	0.00	0.515	175.09	4.82	0.00	0.544	170.68	2.95
2Ea	1.19	0.471	4.22	4.90	2.61	0.521	198.56	4.95	2.04	0.548	226.83	4.28
2Aa	1.19	0.426	204.43	3.03	1.72	0.507	194.67	4.04	1.31	0.527	213.49	5.12
3Ee	0.00	0.495	39.17	4.63	2.82	0.532	169.38	4.95	2.22	0.572	143.34	1.30
3Ae	0.29	0.456	124.81	3.87	0.00	0.516	170.00	5.26	0.00	0.546	167.66	3.34
3Ea	0.66	0.485	29.48	6.30	3.94	0.517	198.54	2.68	3.48	0.551	296.06	2.69
3Aa	1.14	0.441	117.67	2.53	0.76	0.503	184.88	2.75	0.75	0.525	248.12	2.45
4Ee	0.00	0.494	0.00	1.99	2.75	0.532	180.00	5.51	2.29	0.571	180.00	1.66
4Ae	0.55	0.456	180.00	4.05	0.00	0.516	180.00	5.70	0.00	0.546	180.00	3.73
4Ea	1.01	0.478	0.00	3.88	4.02	0.512	180.00	2.34	3.34	0.548	0.00	2.60
4Aa	1.55	0.439	180.00	2.13	1.30	0.496	180.00	2.41	1.07	0.522	0.00	0.63
1mE	0.00	0.479	0.00	5.20	1.41	0.530	180.00	4.03	1.33	0.567	180.00	0.87
1mA	1.31	0.450	0.00	3.05	0.00	0.512	180.00	4.55	0.00	0.536	180.00	4.08
2mEe	1.40	0.498	13.71	5.27	1.80	0.544	153.08	2.10	0.91	0.568	192.36	2.49
2mEa	0.00	0.476	19.70	6.03	1.21	0.530	183.12	2.91	0.74	0.559	237.91	1.53
2mAe	1.94	0.482	24.01	10.11	0.00	0.523	162.75	2.94	0.00	0.550	143.40	1.88
2mAa	0.30	0.438	273.79	1.87	0.77	0.509	198.40	4.00	0.01	0.526	208.79	5.71
3mEe	0.00	0.499	38.89	4.72	1.51	0.537	168.27	4.41	1.33	0.574	143.26	1.28
3mEa	0.67	0.489	30.39	6.46	2.65	0.522	204.12	2.27	2.59	0.533	296.02	2.81
3mAe	1.14	0.468	70.01	3.09	0.00	0.519	171.03	5.13	0.00	0.542	172.41	4.57
3mAa	2.45	0.446	337.38	0.43	1.63	0.490	222.52	7.37	0.63	0.515	234.60	5.67
4mEe	0.00	0.498	0.00	1.79	1.42	0.537	180.00	5.02	1.38	0.573	180.00	1.65
4mEa	1.02	0.481	0.00	3.79	2.71	0.517	180.00	1.72	2.43	0.550	0.00	2.71
4mAe	1.39	0.468	180.00	0.72	0.00	0.519	180.00	5.59	0.00	0.543	180.00	4.86
4mAa	2.43	0.451	0.00	1.48	1.30	0.498	180.00	2.17	6.01	0.498	180.00	2.17

steric energy because the flattening of the ring decreases the 1,3-diaxial repulsions between hydrogens.[54] Therefore, the puckering tendency $Q_{\mathbf{1A}} < Q_{\text{cyclohexane}} < Q_{\mathbf{1E}}$ shows that the larger planarity of **1A** contributes to the reduction of the 1,3 diaxial steric repulsions between the C—H and N—H bonds, which are probably higher than in cyclohexane because C—N bonds are shorter than C—C bonds. On the other hand, the 1,3 interactions between C—H and N—H bonds in **1A** are also probably larger than between C—H bonds and the lone pair in **1E**, so that this form is more puckered than cyclohexane. According to all the aforementioned, the puckering of piperidine rings should be determined by both the presence of steric effects and the delocalization of the lone pair.

According to the HF/6–31G** NBO energy decomposition of the axial/equatorial equilibrium of piperidine (Table V), the different Lewis energies are the main component of $\Delta E_{A/E}$. Because the dipole moments of both conformers are very similar, the electrostatic interactions included in E_{Lew} are probably similar in both forms and the steric interactions will be responsible for the higher E_{Lew} of **1A** (1.35 kcal/mol), as suggested above by the values of Q. However, the final value of $\Delta E_{\mathbf{1A/1E}}$ is reduced because **1A** is stabilized by delocalization (0.6 kcal/mol). The analysis of the components of the second-order Fock matrix shows that

TABLE V.
HF / 6-31G Relative Energies (E_{rel}), Lewis Energies (E_{Lew}), and Hyperconjugation Energies (E_{del}) for Conformers of N-H (1-4) and N-Me (1m-4m) Compounds.**

	E_{rel}	E_{Lew}	E_{del}	μ		E_{rel}	E_{Lew}	E_{del}	μ
1E	0.00	0.00	0.00	0.89	**1m**E	0.00	0.00	0.00	0.60
1A	0.76	1.35	−0.59	1.23	**1m**A	3.59	2.45	1.14	0.88
2Ee	0.00	0.00	0.00	0.91	**2m**Ee	0.00	0.00	0.00	0.60
2Ae	0.88	1.81	−0.93	1.13	**2m**Ea	1.47	3.75	−2.28	0.55
2Ea	3.07	2.92	0.15	0.89	**2m**Ae	2.83	3.32	−0.49	0.79
2Aa	3.53	1.61	1.92	1.16	**2m**Aa	3.54	1.62	1.92	0.80
3Ee	0.00	0.00	0.00	0.87	**3m**Ee	0.00	0.00	0.00	0.54
3Ae	0.67	1.31	−0.64	1.26	**3m**Ea	1.56	−0.62	2.18	0.65
3Ea	1.57	−0.43	2.00	0.99	**3m**Ae	3.51	2.43	1.08	0.90
3Aa	2.62	2.04	0.57	1.21	**3m**Aa	7.16	7.58	−0.42	0.76
4Ee	0.00	0.00	0.00	0.99	**4m**Ee	0.00	0.00	0.00	0.65
4Ae	0.72	1.05	−0.33	1.18	**4m**Ea	2.39	−0.14	2.53	0.56
4Ea	2.46	−0.12	2.58	0.89	**4m**Ae	3.54	2.10	1.44	0.81
4Aa	3.17	0.63	2.54	1.28	**4m**Aa	6.09	1.57	4.52	0.91

N-H Equilibria	$\Delta E_{A/E}$	ΔE_{Lew}	ΔE_{del}	N-Me Equilibria	$\Delta E_{A/E}$	ΔE_{Lew}	ΔE_{del}
1A/**1**E	0.76	1.35	−0.59	**1m**A/**1m**E	3.59	2.45	1.14
2Ae/**2**Ee	0.88	1.81	−0.93	**2m**Ae/**2m**Ee	2.83	3.32	−0.49
2Aa/**2**Ea	0.46	−1.31	1.76	**2m**Aa/**2m**Ea	2.07	−2.14	4.21
3Ae/**3**Ee	0.67	1.31	−0.64	**3m**Ae/**3m**Ee	3.51	2.43	1.08
3Aa/**3**Ea	1.05	2.47	−1.43	**3m**Aa/**3m**Ea	5.60	8.20	−2.60
4Ae/**4**Ee	0.72	1.05	−0.33	**4m**Ae/**4m**Ee	3.54	2.10	1.44
4Aa/**4**Ea	0.72	0.75	−0.03	**4m**Aa/**4m**Ea	3.70	1.71	1.99

C-Me Equilibria	$\Delta E_{A/E}$	ΔE_{Lew}	ΔE_{del}	C-Me Equilibria	$\Delta E_{A/E}$	ΔE_{Lew}	ΔE_{del}
0ma/**0m**e	2.31	0.17	2.14				
2Ea/**2**Ee	3.07	2.92	0.15	**2m**Ea/**2m**Ee	1.47	3.75	−2.29
2Aa/**2**Ae	2.65	−0.19	2.84	**2m**Aa/**2m**Ae	0.71	−1.71	2.42
3Ea/**3**Ee	1.57	−0.43	2.00	**3m**Ea/**3m**Ee	1.56	−0.62	2.18
3Aa/**3**Ae	1.95	0.73	1.21	**3m**Aa/**3m**Ae	3.65	5.14	−1.50
4Ea/**4**Ee	2.45	−0.12	2.57	**4m**Ea/**4m**Ee	2.38	−0.14	2.53
4Aa/**4**Ae	2.45	−0.42	2.87	**4m**Aa/**4m**Ae	2.55	−0.53	3.07

ΔE_{Lew} and ΔE_{del} are the NBO contributions evaluated for the axial/equatorial energy differences of the N-R ($\Delta E_{A/E}$) and C-Me ($\Delta E_{a/e}$) groups. All the values are in kilocalories/mole. HF/6-31G** dipole moments (μ) are in debyes.

the $n_N-\sigma_{C-H}$ and $n_N-\sigma^*_{C-C}$ interactions are the most important energetically. However, none of these interactions is clearly dominant, so delocalization of the lone pair stabilizes both conformers in a similar amount. The higher delocalization in **1A** is due to bond-antibond interactions and in particular to the $\sigma_{C-H}-\sigma^*_{N-H}$ interactions. The increase of population on the antibond σ^*_{N-H} would explain the gain of electronic charge in H7 when passing from **1E** to **1A** (Table VI).

The values of Q and ϕ_2 for methylcyclohexane, where the delocalization of the lone pair does not exist, indicate that the axial conformer **0m**a is flattened mainly in the methyl region, probably to reduce 1,3-diaxial repulsions. The considerable opening of the C7-C1-C2-C3 torsional angle with respect to its value in cyclohexane (7.63°) also contributes to reduce these repulsions (Table VII). On the other hand, the introduction of an equatorial C-Me group hardly modifies the puckering of **0m**e compared to cyclohexane, which suggests that the steric interactions are not increased. Therefore, the small Lewis energy differences between **0m**e and **0m**a (Table V) should indicate similar steric interactions in both conformers and $\Delta E_{0ma/0me}$ mainly arises from E_{del}. The NBO analysis indicates that bond-antibond interactions are responsible for the stabilization by hyperconjugation of

TABLE VI.
HF/6–31G NPA Charges for Axial and Equatorial Conformers of Methylcyclohexane (0m) (R1 = C1, R7 = C7), Piperidine (1) (R1 = N1, R7 = H7), and *N*-Methylpiperidine (1m) (R1 = N1, R7 = C7).**

Atom	R1	C2	C3	C4	R7	H9
0me	−0.2379	−0.4350	−0.4324	−0.4350	−0.6382	0.2107
0ma	−0.2394	−0.4359	−0.4366	−0.4352	−0.6469	0.2162
1E	−0.7493	−0.2132	−0.4450	−0.4384	0.3861	0.1771
1A	−0.7403	−0.2190	−0.4563	−0.4392	0.3751	0.2058
1mE	−0.5715	−0.2125	−0.4412	−0.4373	−0.4098	0.1779
1mA	−0.5735	−0.2151	−0.4567	−0.4384	−0.4143	0.2100

See atom numbering in Figure 1.

the equatorial form. Interactions where C7–C1 takes part are the most important, in particular when the C—C endocyclic bonds are in the trans position to the methyl group ($\sigma_{C7-C1}-\sigma^*_{C2-C3}$ and $\sigma_{C7-C1}-\sigma^*_{C6-C5}$). As a consequence, the population on the σ_{C7-C1} orbital in **0m**e is reduced and the NPA (natural population analysis) charges on C1 and C7 are smaller than in **0m**a (Table VI).

According to NBO, the N-Me equatorial preference in **1m** is larger than in **1** and is due to the

TABLE VII.
HF / 6–31G Torsional Angles Associated to Axial and Equatorial Substituents of Piperidine Rings.**

	7–1–2–3	$\Delta_{7-1-2-3}$	9–2–1–6	$\Delta_{9-2-1-6}$	11–3–2–1	$\Delta_{10-3-2-1}$	13–4–3–2	$\Delta_{13-4-3-2}$
0me	−179.10	1.78	66.67	0.70	−65.76	−0.21	66.15	0.18
0ma	73.60	7.63	67.77	1.80	−66.95	0.98	65.88	−0.09
1E	174.50	8.18	59.89	−6.08	−64.48	−1.49	67.76	1.79
1A	69.30	3.33	67.93	1.96	−67.21	1.24	67.57	1.60
2Ee	175.24	7.44	176.71	5.97	−65.38	−0.59	67.49	1.52
2Ae	69.62	3.65	−178.99	1.67	−67.78	1.81	67.47	1.50
2Ea	175.90	6.78	69.46	3.49	−67.23	1.26	68.40	2.43
2Aa	73.05	7.08	77.23	11.26	−69.61	3.64	68.32	2.35
3Ee	173.91	8.77	59.61	−6.36	−179.92	2.60	68.47	2.50
3Ae	69.20	3.23	67.77	1.80	177.68	5.00	68.17	2.20
3Ea	172.80	9.88	58.20	−7.77	−69.88	3.91	68.86	2.89
3Aa	69.94	3.97	67.06	1.09	−73.29	7.32	68.84	2.87
4Ee	174.73	7.95	60.21	−5.76	−64.38	−1.59	−177.07	−0.25
4Ae	69.48	3.51	68.29	2.32	−67.09	1.12	−177.31	−0.01
4Ea	174.45	8.23	61.02	−4.95	−64.57	−1.40	75.70	9.73
4Aa	68.77	2.80	68.87	2.90	−67.26	1.29	75.40	9.43
1mE	173.93	8.75	62.92	−3.05	−64.69	−1.28	67.51	1.54
1mA	77.46	11.49	66.39	0.42	−67.03	1.06	67.64	1.67
2mEe	176.43	6.25	−179.44	2.12	−66.15	0.18	67.00	1.03
2mEa	169.96	12.72	69.86	3.89	−65.69	−0.28	67.56	1.59
2mAe	75.11	9.14	175.61	7.07	−66.82	0.85	68.26	2.29
2mAa	80.79	14.82	75.90	9.93	−69.22	3.25	68.53	2.56
3mEe	173.42	9.26	62.68	−3.29	−179.85	2.53	68.25	2.28
3mEa	172.41	10.27	61.15	−4.82	−69.62	3.65	68.63	2.66
3mAe	77.51	11.54	66.28	0.31	177.89	4.79	68.24	2.27
3mAa	84.69	18.72	68.40	2.43	−77.48	11.51	70.10	4.13
4mEe	174.11	8.57	63.17	−2.80	−64.59	−1.38	−177.05	−0.27
4mEa	173.78	8.90	63.98	−1.99	−64.78	−1.19	75.39	9.42
4mAe	77.47	11.50	66.72	0.75	−66.90	0.93	−177.23	−0.09
4mAa	77.07	11.10	67.36	1.39	−67.21	1.24	75.80	9.83

See atom numbering in Figure 1. Δ are the differences between the values shown and the corresponding torsions for an axial or equatorial hydrogen in cyclohexane (65.97° and −177.32°, respectively, at the HF/6–31G** level).

increase in E_{Lew} of the axial form **1m**A and to the stabilization by hyperconjugation of the equatorial form **1m**E. The considerable opening of the C7–N1–C2–C3 torsional angle (11.49°) suggests enhanced 1,3-diaxial repulsions, and the Lewis energy of the N-Me axial conformer increases. With regard to the hyperconjugative contribution, the interactions in which the nitrogen lone pair is involved are again stronger but do not dominate in any of the conformers. So, bond–antibond interactions determine the higher delocalization in **1m**E, in particular those contributions involving N-Me, like $\sigma_{C7-N1}-\sigma^*_{C2-C3}$, and hence the charges on N1 and C7 in **1m**E are smaller than those in **1m**A (Table VII). Therefore, according to the NBO method, the origin of ΔE_{del} is similar for methylcyclohexane and *N*-methylpiperidine and confirms that methyl groups in equatorial orientation stabilize mainly because of delocalization. This idea coincides with the electron-donor character of the N-Me and C-Me groups invoked in order to explain the reduction of the experimental ionization potentials of the *N*-methylpiperidines with regard to the corresponding piperidines (e.g., 8.37 and 8.70 eV for **1m** and **1**, respectively).[55]

INFLUENCE OF METHYLATION ON AXIAL/EQUATORIAL EQUILIBRIA OF N-R GROUP

The puckering coordinates for the conformers of **2**, **3**, and **4** show that the geometrical effects due to the N-H and C-Me groups are practically additive (Table III). At the HF/6–31G** level and always with respect to cyclohexane, the Ee conformers are puckered approximately 0.01 Å due to the equatorial position of the N-H group and the Ae conformers are flattened 0.03 Å due to the axial N-H group. In both cases, as expected, the equatorial C-Me group does not contribute to modifying the puckering of the ring. The Aa conformers show the largest variations (Q decreases about 0.04 Å) because the N-H and C-Me axial groups tend to flatten the ring simultaneously. The values of Q for **2m**, **3m**, and **4m** behave in a way similar to those of N-H systems. Slight discrepancies are observed in the Ea conformers and will be discussed in detail below.

As can be seen in Table V, and in accordance with the variations in the puckering, $\Delta E_{A/E}$ for the N-H and N-Me equilibria of conformers with equatorial C-Me (pairs Ae/Ee) are similar to the energy differences in **1** and **1m**. Although minor differences can be observed, the NBO energy contributions for these equilibria are analogous; that is, the axial forms of N-H compounds have higher E_{Lew} but are more stabilized through hyperconjugation, while the axial N-Me compounds have also higher E_{Lew} but are destabilized through hyperconjugation. Only the pair **2m**Ae/**2m**Ee shows an energy difference of 2.83 kcal/mol, notably smaller than that of **1m**A/**1m**E. The puckering amplitude Q for **2m**Ae is larger than for the rest of the Ae conformers because, as suggested by the $\phi_2 = 22.90°$, the region of the equatorial 2-Me is puckered. It should also be noted (Table VII) that the widening of the C7–N1–C2–C3 torsional angle with respect to cyclohexane is smaller than in **1m**A (9.14° vs. 11.49°), and the variation of the C9–C2–N1–C6 torsional angle associated with the equatorial 2-Me group is notably larger than in **0m**e (7.07° vs. 1.78°). These geometrical features suggest the existence of a noticeable interaction between both adjacent methyl groups, which leads to an increase of ΔE_{Lew} up to 3.32 kcal/mol. ΔE_{del} changes its sign compared to **1m** (−0.49 kcal/mol) due to the increase of bond–antibond interactions between the axial N-Me group and the C-H bonds trans disposed. The balance between both contributions is the reduction of the axial/equatorial energy difference for **2m**Ae/**2m**Ee.

The Ea conformers are responsible for the differences observed in the N-H equilibria when the C-Me is in the axial position (pairs Aa/Ea). Hence, $\Delta E_{A/E}$ for **2**Aa/**2**Ea is reduced up to 0.46 kcal/mol and the NBO energy contributions are remarkably different. ΔE_{Lew} changes its sign (−1.31 kcal/mol) in contrast to the rest of the equilibria. The order in E_{Lew} (**2**Ee < **2**Aa < **2**Ae < **2**Ea) indicates a high steric contribution in **2**Ea, which is probably due to the parallel orientation between the N—H bond and a C—H bond of the axial 2-Me group. Due to this interaction, the H7–N1–C2–C3 torsional angle is less widened (6.78° with respect to cyclohexane) than in other equatorial N-H conformers (Table VII), the opening of the C9–C2–N1–C6 torsional angle associated with the axial 2-Me is smaller than in **0m**a (3.49°), and the puckering amplitude Q (0.557 Å, almost determined by the axial 2-Me group) is the smallest one in the N-H equatorial conformers (Table III). Consequently, **2**Ea shows the largest E_{Lew} of the N-H compounds, which indicates that parallel interactions destabilize the equatorial N-H form approximately 2.7 kcal/mol. The influence of parallel interactions between the N—H bond and other adjacent bonds was also discussed for other nitrogen rings with sub-

stituents other than methyl.[39] On the other hand, also in contrast to what happens in the rest of the N-H equilibria, **2**Ea is remarkably stabilized with respect to **2**Aa through hyperconjugation (ΔE_{del} = 1.76 kcal/mol), which is mainly due to the increase of the delocalization of the axial lone pair in the trans oriented C—C_{Me} bond, as reflected in the interaction n_N–σ^*_{C2-C9}.

For the **2m**Aa/**2m**Ea equilibrium, the NBO contributions vary as in **2**. The negative value of ΔE_{Lew} (−2.14 kcal/mol) has the same origin as in **2**Aa/**2**Ea, although **2m**Ea is more destabilized because there are more parallel interactions between the C—H bonds of both methyl groups. On the other hand, the methyl groups in **2m**Aa are as far apart as possible and do not interact with each other. Both effects contribute to reduce ΔE_{Lew}. On the other hand, ΔE_{del} increases by approximately 3 kcal/mol compared to **1m**, because the delocalization in **2m**Ea of the lone pair on the axial C—C_{Me} bond is higher.

In 3-methylpiperidine, the **3**Aa/**3**Ea pair shows NBO contributions of the same sign as **1**, although numerical values are notably different. The E_{Lew} ordering (**3**Ea < **3**Ee < **3**Ae < **3**Aa) suggests that **3**Ea is stabilized and **3**Aa is destabilized. Compared with cyclohexane, **3**Ea is puckered due to the equatorial N-H group so that, contrary to what was expected, the axial 3-Me does not alter the planarity of the ring. Furthermore, the widening of the C10–C3–C2–N1 angle in **3**Ea (3.91°) is smaller than in the axial C-Me in **0m**a, and the H7–N1–C2–C3 torsional angle shows the largest variation (9.88°) of all the N-H equatorial conformers (Table VII). These geometrical modifications indicate that steric effects are reduced in **3**Ea and explain the reduction of E_{Lew}. In other words, 1,3-diaxial repulsions between the 3-Me group and the nitrogen lone pair in **3**Ea are smaller than between C—H and N—H axial bonds in **1**A or are smaller than between a C—H axial bond and an axial C-Me in **0m**a. Apart from this, E_{Lew} for **3**Aa increases due to the 1,3-diaxial repulsions between the N-H and 3-Me groups. Both effects increase ΔE_{Lew} in **3**Aa/**3**Ea up to 2.47 kcal/mol. The hyperconjugative contribution ΔE_{del} (−1.43 kcal/mol) acts in the opposite direction, because methylation in **3**Aa increases the contribution of bond–antibond interactions. The balance between steric and hyperconjugative effects increases $\Delta E_{A/E}$ up to 1.05 kcal/mol.

With respect to **3m**, $\Delta E_{A/E}$ for **3m**Aa/**3m**Ea also increases notably (~ 2 kcal/mol) with regard to **1m** due to the increase in ΔE_{Lew} as a consequence of the large 1,3 repulsions between both axial N-Me and 3-Me groups. As observed in **3**Aa, the larger delocalization of **3m**Aa due to larger bond–antibond interactions slightly compensates for the increase in E_{Lew}. Finally, axial or equatorial methylations in position C4 of the piperidine ring do not affect the equilibria of the N-R group. In **4**, $\Delta E_{A/E}$ for the **4**Ae/**4**Ee and **4**Aa/**4**Ea equilibria are equal (0.72 kcal/mol)/and similar to **1**. The same occurs for **4m** where the $\Delta E_{A/E}$ are similar to those for **1m**.

AXIAL/EQUATORIAL C-Me EQUILIBRIA IN DIFFERENT RING POSITIONS

The axial/equatorial energy differences for the C-Me equilibria are different depending on the position of the ring considered, which suggests that the influence of the heteroatom N1 should differ in each case (Table V). The equilibria of the 2-Me group have been the object of particular experimental attention. Eliel et al.[24] used ^{13}C NMR spectroscopy to find an increase in $\Delta E_{a/e}$ for **2**Ea/**2**Ee with respect to **0m** (2.5 vs. 1.7 kcal/mol), while a ''normal'' value was determined for **2m**Ea/ **2m**Ee (1.7 kcal/mol). They suggested different reasons for both values. On the one hand, $\Delta E_{a/e}$ is larger for **2** because **2**Ea is destabilized due to the shortening of the C—N bond, which reduces the nonbonded distances between the axial 2-Me and the axial hydrogen at C6.[24,56] On the other hand, $\Delta E_{a/e}$ is reduced when passing from **2** to **2m** due to the destabilization of **2m**Ee, because due to the puckering of the ring in the nitrogen region the equatorial N-Me and 2-Me groups are closer than the equatorial N-Me and the axial 2-Me groups of **2m**Ea.[24,56]

Our calculations for **2**Ea/**2**Ee and **2m**Ea/**2m**Ee reproduce the experimental trends and $\Delta E_{a/e}$ decreases when passing from **2** to **2m**. The NBO analysis suggests that $\Delta E_{a/e}$ for **2**Ea/**2**Ee is larger than in **0m** due to the balance between the increase of ΔE_{Lew} and the reduction of ΔE_{del}. One journal referee suggested that the increased Lewis energy differences seem to support Eliel et al.'s argument.[24] However, the torsion angles associated with the axial hydrogen at C6 (H16) do not present variations as large as would be expected if 1,3-diaxial interactions were larger in **2**Ea ($\Delta_{H16-C6-C5-C4} = 2.94°$ and $\Delta_{H16-C6-N1-C2} = -3.75°$ compared to the values in cyclohexane). In addition, strong 1,3-diaxial interactions would also be present in the other 2-Me axial conformer (**2**Aa),

but its Lewis energy is notably smaller than that of **2**Ea. Thus, even though the interaction 2-Me/C6-H16 can increase, it does not seem to be responsible for the increase in ΔE_{Lew} for the **2**Ea/**2**Ee pair. According to the geometrical features discussed in the previous section, the increase of the Lewis energy in **2**Ea could be due to the parallel orientation of the N—H and C—H bonds. With regard to **2m**, calculations also seem to contradict Eliel et al.'s[24] arguments for the normal value of the energy difference of **2m**Ea/**2m**Ee. On the one hand, the order of E_{Lew} (**2m**Ee < **2m**Aa < **2m**Ae < **2m**Ea) indicates that **2m**Ee is not destabilized by steric effects. On the other hand, the puckering at the N-Me region is not increased because Q for **2m**Ee (0.563 Å) is smaller than for **2**Ee (0.570 Å). The NBO results suggest that the origin of $\Delta E_{\mathrm{a/e}}$ in **2m**Ea/**2m**Ee is the same as that in **2**Ea/**2**Ee, although the numerical values are different. Thus, the steric contribution due to the interaction between parallel bonds destabilizes **2m**Ea and ΔE_{Lew} increases (3.75 kcal/mol), although this destabilization is counteracted by an increase of ΔE_{del} (−2.29 kcal/mol) as a consequence of the higher delocalization of **2m**Ea (see also the previous section).

The energy differences for the equilibria of the 3-Me group, **3**Ea/**3**Ee, and **3m**Ea/**3m**Ee are reduced by the same amount with respect to **0m**. According to the NBO energy contributions, as $\Delta E_{\mathrm{a/e}}$ stays almost unaltered, the reduction of $\Delta E_{\mathrm{a/e}}$ is a consequence of the smaller 1,3-diaxial repulsions between the axial 3-Me and the lone pair in **3**Ea and **3m**Ea that reduce ΔE_{Lew} about 0.5 kcal/mol. The other 3-Me equilibria behave in a different manner. For **3**, $\Delta E_{\mathrm{a/e}}$ for **3**Aa/**3**Ae is reduced to 1.95 kcal/mol, because the increase of ΔE_{Lew} by about 0.6 kcal/mol due to larger 1,3-diaxial repulsions in **3**Aa is counteracted by the increase of delocalization by about 0.9 kcal/mol. On the other hand, the energy difference for **3m**Aa/**3m**Ae is approximately 1.7 kcal/mol higher, because ΔE_{Lew} increases even more than in **3** as a consequence of the strong 1,3-diaxial repulsions between methyl groups in **3m**Aa, although this form is also more stabilized by delocalization.

The energy differences for the methyl equilibria of **4** and **4m** are hardly modified with respect to **0m**, and the NBO energy contributions are similar for all the pairs of conformers. ΔE_{Lew} are reduced in all cases because of the opening of the C13–C4–C3–C2 torsional angle (~ 9.5°) associated with the axial 4-Me group, while the bond-antibond interactions $\sigma_{\mathrm{C4-C13}}-\sigma^{*}_{\mathrm{C3-C2}}$ corresponding to the equatorial 4-Me produce an increase in ΔE_{del}. So, the methyl equilibria at C4 are similar to those of **0m**, and the substitution of carbon for nitrogen at position 1 does not affect its behavior appreciably.

Conclusions

The results obtained at several computational levels for the axial/equatorial equilibrium of the N-R group in piperidines indicate that HF calculations using a polarized basis set of medium size like 6–31G** are adequate enough for the prediction of the conformational preferences. Electron correlation considered at the MP2 level is very sensitive to the basis set employed and does not significantly improve the HF results obtained with the larger basis sets. On the contrary, for predicting the axial/equatorial energy differences of the C-Me equilibria, the inclusion of electron correlation becomes necessary because the MP2 values are always approximately 0.5 kcal/mol lower than the HF ones.

Excellent agreement was found between the direct experimental microwave measurements of the axial/equatorial energy difference for piperidine and methylcyclohexane and MP2/6–311 + + G**//MP2/6–31G** + ZPE(HF/6–31G**) calculations. This computational level seems to be adequate to predict refined conformational stabilities in a highly accurate way. According to this, the small discrepancies between the experimental values of energy differences for N-methylpiperidine and for the C-Me equilibria in piperidine rings could suggest the need to revise the interpretation of the experimental data. Experimental energy differences are usually estimated by considering the additivity of methyl group equilibria in different positions of the ring or equal geometries regardless of substitution. Theoretical results for energies and geometries show that these estimates are not always correct, so the data provided in this work could help to improve the interpretations of experimental results and even the molecular mechanics force field for amines of the MM2 and MM3 programs could be refined.

Semiempirical methods should be used with caution if piperidine systems are to be described in a precise way. AM1 and PM3 predict completely

opposite stabilities than the experimental data and *ab initio* calculations. However, the geometries are acceptable, PM3 being slightly better than AM1. MNDO appears to be the most suitable semiepirical method for obtaining relative energies because conformational stabilities are reproduced correctly, even though quantitative agreement with experimental or *ab initio* values is not excellent. However, MNDO geometries are poor because piperidine rings are systematically too flat.

From the existence of geometrical trends related to the delocalization of the nitrogen lone pair and the comparison with the geometries of cyclohexane and methylcyclohexane, it can be concluded that the degree of puckering of piperidine rings depends on both hyperconjugative and steric effects (1,3-diaxial repulsions). The geometrical modifications produced by the introduction of the N-R and C-Me groups in several positions of the cyclohexane ring are practically additive, except for the Ea conformers at positions C2 and C3. However, the relative energy of the conformers for each molecule or the axial/equatorial energy differences corresponding to the N-R or C-Me equilibria are not always additive, mainly at the C2 and C3 positions. The substitution at C4 is the only one that does not noticeably alter the equilibria of the N-R and C-Me groups, because the interactions between them when located in positions 1,4 are very small.

The origin of the stabilities of the different conformers of piperidines was interpreted on the basis of the NBO analysis. The equatorial preference in the N-H equilibria is mainly due to lower Lewis energies, even though this preference is reduced by the larger delocalization of the axial N-H forms because of the more favorable bond−antibond interactions. *N*-Methylation increases the equatorial N-Me preferences because the Lewis energy of the axial N-Me forms increases due to larger 1,3-diaxial interactions. This increase is also reinforced because the equatorial N-Me forms delocalize more than the axial ones, mainly because the higher donor character of the methyl group increases the σ_{N-C} delocalizations on the σ^*_{C-C} in trans orientation. The exceptions are due to the change in the relative importance of some of the factors, for instance due to larger steric interactions as in **3**Aa and **3**mAa, or to larger hyperconjugative contributions as in **2**Ea and **2**mEa. These changes in the NBO energy contributions are responsible for the variations in ΔE observed for the N-R and C-Me equilibria in different positions of the ring.

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